

Long-Acting Theophyllines

LONG-ACTING theophylline preparations, designed for once-a-day dosing in relatively healthy adults who have asthma, have become available for prescription usage in the United States within the past year. These sustained-release medications provide stable therapeutic blood concentrations, effective bronchodilation and bioavailability similar to the twice-a-day theophylline preparations with, for some patients, the added convenience of once-a-day administration. Long-acting theophyllines can usually be given in one daily dose equal in milligrams to the daily dose of a shorter-acting theophylline preparation. Although the primary toxicities of the long-acting theophyllines are those from theophylline in general, so that precautions in methylxanthine administration apply to all types of theophylline preparations, additional precautions pertain to long-acting, once-a-day theophylline preparations.

Smokers metabolize theophylline very quickly and often require twice-a-day administration of the "24-hour" preparations. The elderly, those with congestive heart failure and those who have hepatic dysfunction are at an increased risk for toxic effects due to slow theophylline metabolism and therapy should be started at low doses and their blood concentrations monitored carefully. Manufacturers recommend that a single dose of sustained-release theophylline be given in the morning due to variations in drug levels with posture, activity and food intake. Because very large doses of some theophyllines taken with meals may result in erratic gastrointestinal absorption and unpredictable theophylline blood concentrations, taking the daily dose on awakening—one to two hours before breakfast—may eliminate this potential problem. Twice-a-day preparations may provide more stable blood theophylline concentrations in some patients requiring large theophylline doses.

When acute bronchospasm necessitates urgent theophylline therapy, an immediate-acting theophylline preparation or intravenous administration of aminophylline (theophylline with ethylenediamine) is indicated. Long-acting theophylline preparations should be reserved for long-term theophylline maintenance therapy particularly when improved patient compliance and convenience are of concern. They are well tolerated and may be used safely by monitoring serum theophylline concentrations and clinical responses.

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Neutrophil Chemoattractant Receptors and Inflammation

THE IMPORTANCE of neutrophils (polymorphonuclear leukocytes) in the inflammatory process has been appreci-

ated for more than a century, and yet the mechanisms by which they are able to carry out directional locomotion into sites of tissue inflammation is poorly understood. In the past seven to eight years a great deal of knowledge has been accumulated that indicates that the locomotory or chemotactic ability—as it is most often referred to—of neutrophils is due to the presence of specific cell surface receptors for chemoattractants, that is, chemicals towards which the cells move in a directed manner. There is good evidence that many of the functions that the neutrophils carry out as part of their inflammatory activities—such as migrating into the tissues, engulfing foreign bodies, increasing oxygen metabolism and production of toxic oxygen species and microbial killing—are initiated through receptor-mediated cell activation.

A number of chemoattractant receptor systems have been described on the surface of neutrophils, each of which appears to be separate and non-crossreacting and yet all lead to common pathways of cell activation and must therefore be linked at some postreceptor point.

Receptors for fragments of the fifth component of complement (C5_{fr}) are considered extremely important in directing neutrophils into areas of inflammation where complement activation is felt to be an important aspect of the disease pathophysiology, such as serum sickness, immune vasculitis and cryoglobulinemia. There is also very good evidence that complement receptor-induced neutrophil activation and subsequent pulmonary leukostasis are important in acute lung injuries (shock lung syndrome) associated with trauma or sepsis.

The most extensively studied chemoattractant system is that for synthetic *N*-formylated peptides that are felt to be identical or closely related to naturally occurring bacterial products and thus are important as a model of neutrophilic response to infection. Studies of the formyl peptide receptor system have shown that certain anti-inflammatory agents (especially glucocorticoids) may affect neutrophil function through interactions at the receptor level in addition to their numerous other biologic actions.

Another chemoattractant receptor has been described for a chemotactic factor produced by neutrophils themselves after ingestion of sodium urate or calcium pyrophosphate crystals. Neutrophil activation by this receptor has been postulated to be an important amplification system contributing to the acute inflammation often seen with crystal-induced arthritis.

Most recently, there has been great interest in the role in inflammatory reactions of lipid molecules generated from arachidonic acid, especially the hydroperoxy and hydroxy fatty acids (HPETEs and HETEs) and leukotrienes produced through the action of a lipoxygenase enzyme. In neutrophils, hydroperoxyeicosatetraenoic acids (HPETEs) are further metabolized to a group of compounds termed leukotrienes. The leukotrienes possess potent inflammatory activities and include the sulfidal peptide constituents of slow-reacting substances (C₄, D₄ and E₄) and the dihydroxy leukotriene B₄. Goldman and Goetzl have recently shown a distinct and specific receptor for leukotriene B₄ on neutrophils, and they and others have elucidated the functional responses of neutro-

phils to leukotriene B₄. Although much is still unknown regarding the role of the leukotrienes in inflammation, their potency and ubiquity make them strong candidates as inflammatory mediators or modulators in many disease processes involving recruitment of inflammatory cells. Present efforts are being directed toward the development of specific inhibitors of leukotriene formation. Such agents would be very useful for basic research on the interaction of arachidonic acid metabolites and of great therapeutic potential in the treatment of asthma, rheumatoid arthritis or other related conditions.

Elucidation of increasing numbers of surface receptors for diverse chemoattractants on neutrophils, together with the understanding that the various neutrophil functions are triggered by occupation of these receptors, provides basic information for a clearer understanding of neutrophil function in inflammatory conditions and will likely provide clinicians with more disease-specific and effective therapies in the near future.

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Clinical Significance of Helper/Suppressor T Cells

THE MORPHOLOGICAL determination (typing) of the percent and absolute number of circulating T-“helper” and -“suppressor” lymphocytes has gained widespread popularity with the development of monoclonal antibodies to detect antigens on the surface of different subpopulations of human lymphocytes. In this context, the terms T “helper” and “suppressor,” which are functional terms, are gross oversimplifications. The helper T cells, as detected by the monoclonal antibodies in general use such as T4, contain not only helper cells for immunoglobulin synthesis but also inducer cells for many T-cell functions and even the precursors of some suppressor T cells. Thus, the T-helper/inducer population is really a mixture of related but distinct T cells. These distinctions based on function can be delineated immunologically by other monoclonal antibodies not in general use. Similarly, the suppressor T cells defined by monoclonal antibodies such as T8 comprise a variety of cell types involved in cytotoxicity and in inhibition of immune responses.

The measurement of helper and suppressor T-cell numbers, percents and ratios can be compared with the measurement of different types of leukocytes by differential cell count. Values may be abnormal in many cases but the clinical utility is limited to a very small number of disorders. Furthermore, while the test is very sensitive, it is also nonspecific, being altered in many infectious (especially viral), metabolic, neoplastic, rheumatologic and congenital and acquired immunologic

disorders. Quantitation of helper/suppressor T cells may be clinically useful in certain suspected immunologic disorders. In infants, it can be used to distinguish between transient hypogammaglobulinemia (reduced helper T cells) and congenital agammaglobulinemia (normal helper/suppressor T cells and absent B cells). In adults, T-cell subsets are most often measured in the evaluation of persons suspected of having the acquired immune deficiency syndrome (AIDS). While a reduced number (and percent) of helper T cells with a normal or increased percent of suppressor cells is almost uniformly found in patients who have AIDS, these findings are very nonspecific and, in themselves, not diagnostic. Moreover, altered helper/suppressor T-cell ratios are found after a viral infection and in many sexually active homosexual men who do not have AIDS. Thus, while an abnormal helper/suppressor T-cell ratio is a characteristic immunologic finding useful in confirming the diagnosis of AIDS, it is by no means diagnostic of the disorder. In other adult immunodeficiencies, such as common variable immunodeficiency, T-cell subsets (by the generally used markers) are often abnormal but appear to have no relationship to the in vivo or in vitro functional defects observed.

Measurement of helper/suppressor T cells is not a screening test. In selected patients with possibly abnormal T-cell function, it should be used in conjunction with other tests of immune function such as a battery of delayed hypersensitivity skin tests. It is important to emphasize that patients should not be labelled as having an “immune disorder” or “dysfunction” solely on the basis of an in vitro morphologic determination of helper/suppressor T cells.

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Penicillin-Induced Anaphylaxis

OF AN ESTIMATED 400 to 800 anaphylactic deaths per year in the United States, as many as 75% have been ascribed to penicillin sensitivity. Anaphylaxis may occur in one to four instances per 10,000 patient treatment courses. The death rate is about 1 to 2 per 100,000 patients treated. The oral route appears to be the safest but reactions and even death have occurred from penicillin taken orally. Children are at lower risk than adults.

Penicillin is the only drug whose allergenic metabolites have been identified. The penicilloyl moiety, formed in largest quantity and thus called the major determinant, is responsible most often for accelerated urticarial reactions. A skin test reagent for detecting sensitivity to this determinant is available commercially as penicilloyl-poly-